

Second Trimester Genetic Sonogram- How does it fit in?

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Ultrasound can detect one or more abnormalities in a number of fetuses with aneuploidy, including fetal Down syndrome. This simple fact leads to two related conclusions: 1) detection of certain ultrasound findings must increase the risk for fetal aneuploidy and 2) the absence of such findings must lower the risk.

Systematic evaluation of ultrasound findings known to be associated with fetal aneuploidy, at an appropriate gestational age, has been referred to as a genetic sonogram. Use of a second trimester ultrasound has some advantages over other screening methods (Table 1).

The sensitivity of a genetic sonogram will depend on various factors including the markers sought, gestational age, reasons for referral, and of course the quality of the ultrasound. Despite difference between centers, studies of genetic sonography from referral centers have reported similar detection rates of fetal Down syndrome in the range of 60-90% (Table 2). These relatively high detection rates do not include incorporation of perhaps the most powerful marker of all sonographic markers during the second trimester: absent or hypoplastic nasal bone.

Ultrasound detection of fetal aneuploidy depends on both major or structural defects, and nonstructural or minor markers. Sonographic markers are nonspecific since they are also common in normal fetuses. Detection and false positive rates will vary with the type and number of markers assessed, as well as gestational age.

Major or Structural Abnormalities

Major or structural abnormalities may be seen in up to 20% of fetuses with trisomy 21 during the second trimester, compared to 70-80% of fetuses with trisomy 18 and 90% of fetuses with trisomy 13. Structural abnormalities of trisomy 21 include cardiac defects, hydrops, and cystic hygroma. Rarely, duodenal atresia can also be seen before 20 weeks.

For trisomy 13, malformations of the central nervous system, particularly holoprosencephaly, are the most common specific anomalies reported. Other malformations that have been

detected include facial abnormalities (cyclopia, hypotelorism, cleft lip/palate), renal cystic dysplasia or hydronephrosis, cardiovascular malformations, polydactyly, and clubbed or rocker bottom foot.

The diversity of prenatal sonographic findings reported with trisomy 18 reflects the pathologic findings. Symmetric IUGR, often in association with polyhydramnios or oligohydramnios, may be the initial clue to the presence of trisomy 18 during the third trimester. Common sonographic findings during the second trimester include cystic hygroma, non-immune hydrops, hydrocephalus, spina bifida, diaphragmatic hernia, tracheoesophageal fistula, genitourinary anomalies, cardiovascular malformations, and omphalocele. Subtle or nonstructural findings may include choroid plexus cysts, brachycephaly or "strawberry" shaped head, vermian agenesis, small bowel-containing omphalocele, clenched hands, clubbed feet, and single umbilical artery.

Triploidy is marked by in utero growth retardation (IUGR), typically in association with oligohydramnios. Head/body discordancy is also typical. Placental abnormalities of hydatidiform degeneration or hydropic changes are present in most cases in which the extra haploid set of chromosomes is paternal in origin, but are much less common with a maternal origin. The placenta may appear thickened or demonstrates cystic changes on sonography. However, these findings are highly variable and are not specific for triploidy. Sonographic identification of specific anomalies is often difficult in the presence of marked oligohydramnios. Central nervous system malformations are the most frequent specific malformations identified and are present in most fetuses with triploidy who survive to term. Other anomalies that may be detected include spina bifida, omphalocele, and cardiovascular malformations.

Sonographic Markers

A number of potential markers have been described in association with major chromosome abnormalities during the second trimester (Table 3). These markers are more important for

detection of fetal Down syndrome compared to other major aneuploidies.

Not all sonographic markers are equal. The most useful markers have a high detection rate but a low false rate among normal fetuses. This can be reflected by a higher likelihood ratio, which is simply the detection rate divided by the false positive rate. Combining the age related risk (or biochemical screen risk) with the likelihood ratios derived from the genetic sonogram has been termed the "age adjusted ultrasound risk assessment" (AAURA).

The following sections discuss some of the potential ultrasound markers in greater detail. Following this discussion, methods for using AAURA are described for both increasing and reducing the risk of fetal aneuploidy following a genetic sonogram.

Nuchal Thickening

Redundant skin at the back of the neck is a characteristic clinical feature of infants with trisomy 21 and was first reported by Dr. Langdon Down in 1866. Benacerraf and co-workers were the first to report the sonographic correlate of this clinical feature in terms of nuchal thickening, and thus began the search for other ultrasound markers. Nuchal thickening remains one of the most sensitive and important markers of trisomy 21 during the second trimester. Indeed, while centers may vary the other criteria utilized, virtually all centers use nuchal thickening as a marker for trisomy 21. Although the sensitivity and false positive rates will vary with gestational age and the exact criteria for a positive scan, sensitivities in the range of 20-40% are most common. Sensitivities of nuchal thickening for detection of trisomies 18 and 13 are uncertain.

Nuchal thickening during the second trimester should be clearly distinguished from nuchal translucency during the first trimester. Nuchal thickening performed during the second trimester is obtained in an axial or slightly oblique plane that includes the cisterna magna. Measurements of the entire soft tissue area outside the calvarium are included. In contrast, nuchal translucency in the first trimester is performed in a midline longitudinal plane and only the sonolucent space is measured (inner to inner).

The criteria for increased nuchal thickening vary between centers. Based on early experience, Benacerraf et al suggested a threshold of 6 mm or more after 15 weeks indicated a high risk for trisomy 21. However, prospective studies have suggested that 5 mm is

a better threshold and results in improved sensitivity with only slight increase in the false positive rate and Benacerraf has also adopted the 5 mm cutoff. As a further refinement, a number of studies have now confirmed that normal nuchal thickness varies with gestational age, suggesting that gestational-age specific criteria should be utilized rather than a single cut off. These methods include observed to expected, observed minus expected, or comparison of nuchal thickness with other biometry such as biparietal diameter, or fur/humerus length. Use of multiple of the median data, comparing the actual nuchal measurement with the expected measurement would permit calculation of likelihood ratios and also permit integration with maternal serum biochemical markers for a combined risk. Bahado-Singh and co-workers have reports multiples of the median and estimated likelihood ratios.

Hyperechoic Bowel

Hyperechoic bowel was the second ultrasound marker to be reported in association with trisomy 21. Like other nonstructural markers, hyperechoic bowel is non-specific and is most commonly observed in normal fetuses. However, it is observed with increased frequency among fetuses with aneuploidy, including trisomy 21. Hyperechoic bowel has also been reported in association with bowel atresia, congenital infection, and rarely with meconium ileus secondary to cystic fibrosis. An increased risk of IUGR, fetal demise, and placental-related complications is also recognized with hyperechoic bowel.

Hyperechoic bowel is not as useful as many of the other markers for detection of fetal Down syndrome. Although the likelihood ratio is relatively high because of the low false positive rate, the sensitivity is relatively low when hyperechoic bowel is the only abnormality. Also, detection of hyperechoic bowel is a subjective finding increases with higher transducer frequencies.

Skeletal abnormalities

A characteristic of children with trisomy 21 is short stature, associated with disproportionately short proximal long bones (femur and humerus). Limb shortening can also be detected in some fetuses with trisomy 21 during the second trimester. However there is a large overlap in bone measurements between affected and normal fetuses. Shortened humerus

length appears to be a slightly more specific indicator than shortened femur length. Results probably vary with gestational age, ethnic groups, possibly fetal gender, and the criteria utilized, as well as systematic differences in long bone measurements. Despite these variables, this marker is commonly utilized at screening centers.

The most commonly used method has been to treat limb shortening as categorical variable using a cutoff of observed to expected limb lengths, typically in the range of 89-91% of expected lengths. More sophisticated models treat limb shortening as a continuous variable and convert each value into multiples of the median. When used in this way, limb shortening can be integrated with risks from biochemical screening.

Other skeletal abnormalities associated with trisomy 21 are clinodactyly (shortened middle phalanx of the 5th finger) and widened pelvic angle. Although both are well known clinical features of trisomy 21, these can be difficult to assess on second trimester sonography and so are not typically included in most screening programs.

Skeletal abnormalities are also prominent features of trisomies 13 and 18. Trisomy 13 characteristically shows structural postaxial polydactyly and clubbed or rocker bottom feet. Common skeletal abnormalities of trisomy 18 include clenched hands, often with overlapping digits, radial aplasia or limb shortening, and club feet.

Renal abnormalities

Mild pyelectasis (hydronephrosis) has been associated with an increased risk of aneuploidy,⁹ primarily trisomy 21, but is also a relatively common finding during routine obstetric ultrasound. The prevalence of pyelectasis undoubtedly varies with gestational age even during the time of second trimester scans (14-22 weeks), although this variable has not been evaluated in detail. Renal pyelectasis is measured as the fluid filled renal pelvis in an anterior-posterior dimension. We prefer measurement when the kidneys and spine are oriented toward or away from the transducer rather than to the side. The threshold for a positive scan varies between centers but the most common criteria are > 3 , > 3.5 , or ≥ 4 mm. Ideally, gestational age dependent criteria might be utilized in the future. Using a cutoff of > 3 mm, we observe pyelectasis in about 3% of normal fetuses at our center. Snijders and Nicolaides estimate that mild pyelectasis

increases the risk of trisomy 21 by 1.6 fold over the baseline risk. Our own analysis is consistent with this risk, although this risk may not be increased when pyelectasis is isolated.

Renal abnormalities may also be seen with other aneuploidies, especially trisomy 13. These may include hydronephrosis or renal dysplasia with enlarged, echogenic kidneys.

Echogenic intracardiac focus (Echogenic intracardiac focus, or papillary muscle calcification)

Echogenic intracardiac foci (EIF) is a common finding during the second trimester, observed in 3-4% of normal fetuses. The prevalence among normal fetuses appears to be significantly higher among Asian populations, in the range of 10-15%. Shipp et al. found EIF three times more often among Asian patients compared to Caucasians.

In the first two ultrasound reports of EIF and aneuploidy, Bromley et al. detected EIF in 4.7% (62 of 1312) of controls compared to 18% (4 of 22) of those with trisomy 21, and Lehman et al. reported EIF in 39% of fetuses with trisomy 13 before 20 weeks. A number of studies have now confirmed an association between EIF and trisomy 21, although some studies have failed to show this association. The likelihood ratio of EIF for trisomy 21 as an isolated finding has been estimated in the range of 1 to 4.2

Because EIF is a subjective finding, its detection depends on a variety of factors including resolution of the ultrasound equipment, technique, thoroughness of the exam, and the sonographer's experience. Fetal position is also important since intracardiac foci are best visualized when the cardiac apex is oriented toward the transducer. Despite these variable factors, similar detection rates of EIF from different studies suggest that experienced sonographers can largely agree on its presence or absence.

As another variable, the severity and multiplicity of EIF may be important when considering genetic amniocentesis. Bettelheim et al found EIF located in the left ventricle in 96% of cases, combined left and right ventricle in 4.3%, and isolated to the right ventricle in just 0.7% (1 of 150). Bromley et al concluded that right-sided and bilateral EIF combined together had approximately a two-fold greater risk for aneuploidy compared to left-sided foci, and others have also found that echogenic foci involving both ventricles are more associated with aneuploidy.

We have found that EIF is the single most common sonographic marker in both fetuses with Down syndrome, and in normal fetuses. Therefore, EIF is common among low risk patients and should not be over emphasized among such patients. At the same time, EIF should not be ignored, especially among patients who are considered at increased risk from maternal age or biochemical screening.

We detected EIF in 23.8% of fetuses with Down syndrome compared to 4.4% of controls, corresponding to a positive likelihood ratio of 5.3. Similarly, a meta-analysis of 11 studies (51,831 pregnancies and 333 Down syndrome cases) by Sotirarides and colleagues, showed sensitivity of 26% (95% confidence interval 19, 34) and false positive rate of 4.2% (95% confidence interval 2.8-7.8), with a positive likelihood ratio of 6.2. These two studies suggest that EIF increases the risk of fetal Down syndrome in the range of 5-6 fold. However, if all other markers appear normal, then the actual risk of EIF is reduced, in the range of 1-2 fold.

Choroid plexus cysts

Like other sonographic markers, choroid plexus cysts are a relatively common variant during the second trimester, are transient, and have no known affect on fetal development. Unlike some of the other potential markers (nuchal thickening, hyperechoic bowel), there is no known adverse outcome when the karyotype is normal.

Choroid plexus cysts have been the object of considerable interest and debate because of their association with fetal aneuploidy, notably trisomy 18. Snijders et al. found choroid cysts in 50% of fetuses with trisomy 18 and 1% of karyotypically normal fetuses. This would equate to an overall high likelihood ratio of 50. However, if the cysts were apparently isolated, the risk was only marginally increased. The presence of one other abnormality increased the risk of trisomy 18 to about 20x the baseline risk. The authors suggest that maternal age should be main factor in deciding whether or not to offer fetal karyotyping when isolated choroid plexus cysts are detected. Similar findings have been reported by a number of other authorities, indicating that isolated choroid plexus cysts in low risk women are not associated with an increased risk of aneuploidy.

Accumulative data strongly suggest that larger choroid plexus cysts (> 1 cm) further increase the risk of trisomy 18. Such large cysts undoubtedly take longer to resolve, supporting observations that delayed resolution of choroid

cysts carry an increased risk for trisomy 18. Whether the cysts are unilateral or bilateral does not appear to be significant, although it is probably true that large cysts also tend to be bilateral.

While an association between choroid plexus cysts and trisomy 18 has been clearly established, a possible link with trisomy 21 has been controversial. Bromley et al. found that isolated choroid plexus cysts are not associated with trisomy 21. Our own analysis suggests that choroid cysts are seen more commonly in fetuses with trisomy 21, but not as isolated findings. In fact, isolated choroids plexus cysts actually reduced the risk for fetal aneuploidy, but not as much as if the ultrasound had been entirely normal (Likelihood ratio 0.7 vs. 0.36).

Therefore, we believe that choroid cysts in combination with other markers may further increase the risk for trisomy 21. As an isolated finding following a high quality ultrasound, and assuming the patient is otherwise considered at low risk for fetal aneuploidy, we believe that detection of choroid plexus cysts should not alter obstetric management. Additional reassurance can be obtained by correlating ultrasound findings with serum biochemical markers. Because choroid cysts always resolve, a followup ultrasound is also of no value in decision making, unless it is to detect other abnormalities that were previously missed (for example, cardiac defects).

Hypoplastic Nasal Bone

Hypoplastic or absent nasal bone is potentially one of the most important markers for fetal Down syndrome during the second trimester. Ultrasound and pathologic data suggest that the nasal bone will be absent or hypoplastic in approximately 30-50% of affected cases. In a pathologic study, Stempfle and colleagues found that ossification of the nasal bones was absent in one quarter of trisomic fetuses, regardless of gestational age. Another postmortem study by Tuxen et al. showed that among 33 fetuses with Down syndrome, 10 (30%) had bilateral (n=8) or unilateral (n=2) absence of the nasal bone.

Bromley et al. found that among fetuses with Down syndrome, 6 (37%) of 16 did not have detectable nose bones, compared with 1 (0.5%) of 223 control fetuses. The detection rate was increased when evaluating a hypoplastic nasal bone compared to an absent nasal bone. They suggest that a biparietal diameter–nasal bone length ratio of 11 or more could detect 69%

of fetuses with Down syndrome compared with 5% of euploid fetuses.

Cicero and colleagues also evaluated the nasal bone during the second trimester. They found the nasal bone was hypoplastic in 21/34 (61.8%) fetuses with trisomy 21, compared to 12/982 (1.2%) chromosomally normal fetuses. In 3/21 (14.3%) trisomy 21 fetuses with nasal hypoplasia there were no other abnormal ultrasound findings. In the chromosomally normal group, hypoplastic nasal bone varied with ethnicity, seen in only 0.5% of Caucasians but 8.8% of Afro-Caribbeans. The likelihood ratio for trisomy 21 for hypoplastic nasal bone was 50.5 (95% CI 27.1-92.7) and for present nasal bone it was 0.38 (95% CI 0.24-0.56).

Based on this limited data, it appears clear that an absent nasal bone is more worrisome for fetal aneuploidy, but that the detection rate is higher when a hypoplastic nasal bone is diagnosed. The false positive rate appears to be low in Caucasian populations (less than 1%) but is higher among Asian and black populations. The likelihood ratio for absent or hypoplastic nasal bone may be as high as 30-50, making it the most powerful of the soft markers for detection of fetal Down syndrome.

Abnormalities of the Central Nervous System / Mild Ventricular Dilatation

Major or structural abnormalities of the central nervous system include holoprosencephaly, agenesis of the corpus callosum, Dandy-Walker malformation, vermian agenesis, and neural tube defects. These types of abnormalities significantly increase the risk of aneuploidy, but not trisomy 21.

Mild ventricular dilatation deserves separate comment because it has been associated with trisomy 21 as well as other aneuploidy. The size of the lateral ventricles remains relatively constant throughout gestation with a mean diameter 6.1 +/- 1.3 mm with slightly larger ventricles in males than females (6.4 mm vs 5.8 mm). Mild ventriculomegaly is suspected when the atrial diameter reaches 10 mm. Early ventricular dilatation may also appear as visibly enlarged ventricles with separation of the choroid from the ventricular wall, yet the ventricle measures less than 10 mm in diameter. In this case, the choroid appears to "dangle" in the ventricle; this is a good visual clue to enlargement. An abnormal relationship is defined as a separation of 3 mm or more between the choroid and the medial ventricular wall.

We have categorized mild/borderline ventricular dilatation as an ultrasound marker rather than a major defect since it is most commonly observed in normal fetuses but increases the risk for other anomalies and chromosome abnormalities. It is more likely to be seen as a normal variant later in the second trimester (after 20 weeks), in male fetuses, and fetuses who are large for gestational age. In a series by Bromley et al, 12% (5 of 43) with mild ventriculomegaly (ventricular diameter 10-12 mm) had abnormal karyotypes (3 trisomy 21, 2 trisomy 18) although all of these showed other findings. The risk when ventricular dilatation is the only abnormality remains uncertain.

Other Potential Markers

A number of other potential markers of fetal aneuploidy have been proposed. These include widened pelvic angle, shortened frontal lobes, small ears, clinodactyly, pericardial effusion, and right-left disproportion of the heart, and hypoplastic nasal bone, among others. Another potential marker for trisomy 21, although not related to fetal anatomy, is unfused amnio and chorion after 14 weeks.

RISK ASSESSMENT

The apriori risk for fetal aneuploidy can be modified based on the presence or absence of sonographic markers. A quantitative method that provides individual risk assessment has been termed Age Adjusted Ultrasound Risk Assessment (AAURA). The ultrasound markers are not considered equally, but rather "weighted" by the strength of individual findings, expressed as likelihood ratios. There is general agreement about the range of likelihood ratios from large series (Table 4). The post priori risk is estimated by these likelihood ratios and the apriori risk based on maternal age.

A further modification of the AAURA method was proposed by Nicolaides et al. He suggests using the overall positive and negative likelihood ratios for each of the ultrasound markers utilized, rather than using likelihood ratios as isolated markers (Table 5). One advantage of this method is that it can more easily account for differences in the panel of markers utilized.

Using AAURA, both the sensitivity of fetal Down syndrome and the false positive rate increase with maternal age. Importantly, AAURA helps to minimize the overall false

positive screen among younger women by assigning relatively low likelihood ratios to minor findings and incorporating a priori risk based on maternal age. As a result, AAURA was falsely positive in only 4% of women under age 35.

Reduction of Risk

Because ultrasound markers increase the risk of fetal Down syndrome, it follows that absence of those markers will reduce the risk of fetal Down syndrome. Reduction of risk is commonly sought, especially among women 35 or older who would like to avoid genetic amniocentesis.

Although using a normal ultrasound for reduction of risk may be applied to all women, it is most useful for women in an intermediate age group, ages 34-40, or for women with intermediate risk based on biochemical screen (risk 1:100 or less risk). To what degree the risk is reduced depends on a variety of factors including the number and type of criteria utilized, individual thresholds, and, undoubtedly, the gestational age of the scan. Despite differences between centers, most recent studies (Tables 3,4) suggest a likelihood ratio in the range of .03 – 0.4 following a normal ultrasound. These likelihood ratios correspond to a 60-70% reduction of risk. Other studies have found 80% or even 90% reduction of risk using ultrasound alone.

Correlation with Biochemical Screen

Second trimester biochemical screening alone has a similar detection rate to second trimester genetic sonogram. Using two or three markers (alpha-fetoprotein and free beta HCG with or without estriol) yields a detection rate in of 60-70% and more recent addition of a fourth marker (inhibin-A) results in detection rates of approximately 75%.

There is good reason to believe that the combination of maternal serum biochemical markers and fetal ultrasound provides more effective screening for Down syndrome than either approach alone. Certainly that has been proven to be true in the first trimester

If ultrasound and biochemical screening are utilized together or in tandem, it is important to know whether the markers are independent. Available data suggests that the markers are largely independent although Souter et al. found some weak associations. Biochemical and ultrasound markers have also been found to be independent during the first trimester. Both

biochemical and ultrasound markers are also independent of maternal age.

Absence or minimal correlation in both affected and unaffected pregnancies indicates that an ultrasound marker and a serum test can be used as independent modifiers of risk. Based on high detection rates for both second trimester genetic sonogram and second trimester biochemistry, using both screening should result in detection rates of over 90%. It is clear that a combined risk estimate using both ultrasound and biochemistry could be more effective than using them independently and also result in lower false positive rates. To date, however, few studies have evaluated the effectiveness of combining ultrasound and biochemistry in the second trimester.

Bahado-Singh and colleagues have shown that even incorporating simple biometric data from ultrasound can significantly improve the performance of second trimester biochemical screening. Similarly, Benn and colleagues found that a second-trimester quadruple serum screen combined with measurements of the biparietal diameter, femur length, humerus length, and nuchal fold could achieve 90% sensitivity with a 3.1% false-positive rate. Pinette et al. also found that incorporation of sonographic markers can result in a substantial reduction in the false positive rate of second trimester biochemical screening, without reduction in the detection rate.

There is every reason to believe that there will be further developments in combining ultrasound and biochemical markers in the future and this should continue to improve second trimester screening.

SUMMARY

A variety of ultrasound findings can be identified in fetuses with fetal aneuploidy. Typical findings vary with both the chromosome abnormality and gestational age at time of the ultrasound exam. The presence of ultrasound markers increases the risk for fetal aneuploidy while a normal ultrasound reduces the risk.

Second trimester genetic sonography, when performed at referral centers by experienced sonographers, has been found to have a high detection rate for trisomy 21, in the range of 60-90%. Because ultrasound markers also appear to be independent of maternal age and biochemical screening, these can be utilized together. The combination of 2nd trimester ultrasound and biochemical screen should have a detection rate of over 90%. Therefore, 2nd trimester screening

is similar in performance to first trimester screening.

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Table 1. Advantages of 2nd trimester genetic sonogram compared to other screening methods

Wide range of gestational age: 14-22 weeks
 Large number of potential markers
 Ability to also detect structural defects
 No other test will replace the value of 2nd trimester anatomic survey
 Both patients and referring physicians believe what they can see

Table 2. Summary of some of the studies using second trimester ultrasound in screening for trisomy 21.

| Author | Total No | No. T 21 | Criteria | GA | Sens | FP Rate | LR | LR negative |
|----------------------|-----------------|----------|--|----|-----------------|---------|-----------|--------------|
| Benacerraf 1994 | 106 controls | 45 | Ultrasound | | 14-21 | 73% | 4% | 18.3 0.28 |
| DeVore 1995 | 1028 | 15 | Ultrasound + Fetal echo. With color doppler | | (17.4) | 87% | 7.4% | 11.8 0.14 |
| Nadel 1995 | 694 controls | 71 | Ultrasound | | 14-21 | 80% | 4% | 20 0.2 |
| Bahado-Singh 1996 | 4079 | 40 | Ultrasound | | 15-24 (17.3) | 70.6% | 14% | 5 0.34 |
| Bahado-Singh 1998 | 3278 | 24 | Ultrasound | | 15-24 (16.7) | 60% | 4.5% | 13.3 0.41 |
| Nyberg 1998 | 930 controls | 142 | Ultrasound + Age (AAURA) | | 14-21 (16.8) | 74% | 14.7 % | 5 0.3 |
| Deren 1998 | 3838 | 44 | Ultrasound | | 15-24 | 63% | 12.8 % | 4.9 0.42 |

| | | | | | | | | |
|--------------------|------|----|------------|-----------------|-------|-----------|------|------|
| Verdin 1998 | 459 | 11 | Ultrasound | 14-24 (17) | 81.8% | 9.8% | 8.3 | 0.2 |
| Vintzileos 1999 | 1835 | 34 | Ultrasound | 15-24 (19.2) | 82% | 13% | 6.3 | 0.2 |
| Sohl 1999 | 2743 | 55 | Ultrasound | 14-24 (17.3) | 67.3% | 19.4 % | 3.5 | 0.41 |
| Vergani 1999 | 920 | 22 | Ultrasound | 14-22 (17) | 59.2% | 5.3% | 11.1 | 0.43 |

LR of Positive Scan = Sensitivity / False Positive Rate

LR of Normal Scan = False Negative Rate/ Specificity

Table 3. Summary of the most common ultrasound findings of aneuploidy during the second trimester

| | Trisomy 21 | Trisomy 18 | Trisomy 13 |
|---------|---|--|--|
| Major | Cardiac defects Duodenal atresia Cystic hygroma Hydrops | Cardiac defects Spina bifida Cerebellar dysgenesis Micrognathia Diaphragmatic hernia Omphalocele Clenched hands/ wrists Radial aplasia Club feet Cystic hygroma | Cardiac defects CNS abnormalities Facial anomalies Cleft lip/palate Urogenital anomalies/ Echogenic kidneys Omphalocele Polydactyly Rocker bottom feet Cystic hygroma |
| Markers | Nuchal thickening Hyperechoic bowel EIF Right/Left cardiac disproportion Shortened limbs Pyelectasis Mild ventriculomegaly Widened pelvic angle Mild ventriculomegaly Shortened frontal lobe Clinodactyly Widened sandal gap Absent or hypoplastic nasal bone | Choroid cysts Brachycephaly Shortened limbs IUGR Single umbilical artery | EIF Mild ventriculomegaly Pyelectasis IUGR Single umbilical artery |

EIF= echogenic intracardiac focus

Table 4. Comparison of likelihood ratios reported for sonographic markers of fetal aneuploidy from two centers and from a meta-analysis study (Smith-Bindaman et al)

| Sonographic Marker | Nyberg et al. | Bromley et al | Smith-Bindman et al. |
|-------------------------------|----------------|---------------|----------------------|
| | LR (95% CI) | LR | LR (95% CI) |
| Nuchal Thickening | 11.0 (5.5-22.) | 12 | 17 (8-38) |
| Hyperechoic bowel | 6.7 (2.7-16.8) | | 6.1 (3-12.6) |
| Short Humerus | 5.1 (1.6-16.5) | 6 | 7.5 (4.7-12) |
| Short Femur | 1.5 (0.8-2.8) | 1 | 2.7 (1.2-6) |
| Echogenic Intracardiac Focus* | 1.8 (1.0-3.) | 1.2 | 2.8 (1.5-5.5) |
| Pyelectasis | 1.5 (0.6-3.6) | 1.3 | 1.9 (0.7-5.1) |
| Normal ultrasound | 0.36 | 0.2 | |

- not applied to Asian populations

Also, see AAURA excel file at www.fetalscreening.com

Table 5. Overall likelihood ratios proposed by Nicolaides et al (2003) based on data from Nyberg et al (2001) and Bromley et al (2002)

| Trisomy 21 | Positive LR (95% CI) | Negative LR (95% CI) | LR For isolated marke |
|-------------------------------|-------------------------|-------------------------|--------------------------|
| Nuchal Thickening | 53.05 (39.37-71.26) | 0.67 (0.61-0.72) | 9.8 |
| Short humerus | 22.76 (18.04-28.56) | 0.6 (0.62-0.73) | 4.1 |
| Short femur | 7.94 (6.77-9.25) | 0.62 (0.56-0.67) | 1.6 |
| Pyelectasis | 6.77 (5.16-8.8) | 0.85 | 1 |
| Echogenic Intracardiac Focus* | 6.41 (5.15-7.9) | 0.75 (0.69-0.8) | 1.1 |
| Echogenic bowel | 21.17 (14.34-31.06) | 0.87 (0.83-0.91) | 3 |
| Major defect | 32.96 (23.90-43.28) | 0.89 (0.74-0.83) | 5.2 |

